

08/476567

attachment to
Paper # 4

=> s glutamine synthetase
6466 GLUTAMINE
1981 SYNTHETASE
L1 94 GLUTAMINE SYNTHETASE
(GLUTAMINE (W) SYNTHETASE)

=> s l1 and vector?

51795 VECTOR?

L2 49 L1 AND VECTOR?

=> d l2,1-49,cit,ti

1. 5,541,310, Jul. 30, 1996, Herbicide resistant plants; Eric R. Ward, et al., 536/23.6; 435/240.2, 240.4, 252.3, 320.1 [IMAGE AVAILABLE]

US PAT NO: 5,541,310 [IMAGE AVAILABLE] L2: 1 of 49
TITLE: Herbicide resistant plants

2. 5,532,142, Jul. 2, 1996, Method of isolation and purification of fusion polypeptides; Stephen A. Johnston, et al., 435/69.1, 69.7, 219 [IMAGE AVAILABLE]

US PAT NO: 5,532,142 [IMAGE AVAILABLE] L2: 2 of 49
TITLE: Method of isolation and purification of fusion polypeptides

3. 5,516,652, May 14, 1996, DNA encoding prostaglandin receptor IP; Mark Abramovitz, et al., 435/69.1, 240.1, 240.2, 252.3, 254.11, 320.1; 530/350; 536/23.1 [IMAGE AVAILABLE]

US PAT NO: 5,516,652 [IMAGE AVAILABLE] L2: 3 of 49
TITLE: DNA encoding prostaglandin receptor IP

4. 5,510,253, Apr. 23, 1996, Plants resistant to infection by PLRV; Timothy A. Mitsky, et al., 435/172.3, 69.1, 240.4, 320.1; 536/23.72; 800/205, DIG.40, DIG.42 [IMAGE AVAILABLE]

US PAT NO: 5,510,253 [IMAGE AVAILABLE] L2: 4 of 49
TITLE: Plants resistant to infection by PLRV

5. 5,503,999, Apr. 2, 1996, Virus resistant plants; Joseph M. Jilka, et al., 435/172.3, 69.1; 536/23.1, 23.72, 24.1; 800/205, DIG.40, DIG.42, DIG.43, DIG.44 [IMAGE AVAILABLE]

US PAT NO: 5,503,999 [IMAGE AVAILABLE] L2: 5 of 49
TITLE: Virus resistant plants

6. 5,500,361, Mar. 19, 1996, .beta.-ketoacyl-ACP synthetase II genes

from plants; Anthony J. Kinney, 435/172.3, 69.1, 71.1, 240.4; 536/23.6; 800/205, 250, 255, DIG.69 [IMAGE AVAILABLE]

US PAT NO: 5,500,361 [IMAGE AVAILABLE] L2: 6 of 49
TITLE: .beta.-ketoacyl-ACP synthetase II genes from plants

7. 5,496,934, Mar. 5, 1996, Nucleic acids encoding a cellulose binding domain; Oded Shoseyov, et al., 536/23.7; 435/252.3, 320.1; 536/23.1, 24.33 [IMAGE AVAILABLE]

US PAT NO: 5,496,934 [IMAGE AVAILABLE] L2: 7 of 49
TITLE: Nucleic acids encoding a cellulose binding domain

8. 5,495,007, Feb. 27, 1996, Phloem-specific promoter; Gary A. Thompson, et al., 536/24.1; 435/172.3, 320.1; 536/23.6; 800/205; 935/35 [IMAGE AVAILABLE]

US PAT NO: 5,495,007 [IMAGE AVAILABLE] L2: 8 of 49
TITLE: Phloem-specific promoter

9. 5,489,520, Feb. 6, 1996, Process of producing fertile transgenic zeamays plants and progeny comprising a gene encoding phosphinothricin acetyl transferase; Thomas R. Adams, et al., 435/172.3, 172.1, 240.45, 240.5; 536/23.7; 800/205, DIG.56 [IMAGE AVAILABLE]

US PAT NO: 5,489,520 [IMAGE AVAILABLE] L2: 9 of 49
TITLE: Process of producing fertile transgenic zeamays plants and progeny comprising a gene encoding phosphinothricin acetyl transferase

10. 5,468,845, Nov. 21, 1995, Antibodies to osteogenic proteins; Hermann Oppermann, et al., 530/387.9, 350 [IMAGE AVAILABLE]

US PAT NO: 5,468,845 [IMAGE AVAILABLE] L2: 10 of 49
TITLE: Antibodies to osteogenic proteins

11. 5,464,937, Nov. 7, 1995, Type II Interleukin-1 receptors; John E. Sims, et al., 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,464,937 [IMAGE AVAILABLE] L2: 11 of 49
TITLE: Type II Interleukin-1 receptors

12. 5,457,182, Oct. 10, 1995, FK-506 cytosolic binding protein, FKBP12.6; Gregory J. Wiederrecht, et al., 530/402; 435/7.8, 69.1, 233; 530/350, 413 [IMAGE AVAILABLE]

US PAT NO: 5,457,182 [IMAGE AVAILABLE] L2: 12 of 49

TITLE: FK-506 cytosolic binding protein, FKBP12.6

13. 5,447,913, Sep. 5, 1995, Therapeutic uses of bactericidal/permeability-increasing protein dimer products; William S. Ammons, et al., 514/12, 21; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,447,913 [IMAGE AVAILABLE] L2: 13 of 49
TITLE: Therapeutic uses of bactericidal/permeability-increasing protein dimer products

14. 5,427,940, Jun. 27, 1995, Engineered cells producing insulin in response to glucose; Christopher B. Newgard, 435/240.2; 424/520; 435/4, 6, 69.1, 172.1, 172.2, 172.3, 320.1; 530/303, 350, 389.2, 397 [IMAGE AVAILABLE]

US PAT NO: 5,427,940 [IMAGE AVAILABLE] L2: 14 of 49
TITLE: Engineered cells producing insulin in response to glucose

15. 5,420,247, May 30, 1995, Leukemia inhibitory factor receptors and fusion proteins; David P. Gearing, et al., 530/350, 387.3, 388.23, 391.1, 402; 536/23.51 [IMAGE AVAILABLE]

US PAT NO: 5,420,247 [IMAGE AVAILABLE] L2: 15 of 49
TITLE: Leukemia inhibitory factor receptors and fusion proteins

16. 5,420,019, May 30, 1995, Stable bactericidal/permeability-increasing protein muteins; Georgia Theofan, et al., 435/69.1, 252.3, 320.1; 530/350; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,420,019 [IMAGE AVAILABLE] L2: 16 of 49
TITLE: Stable bactericidal/permeability-increasing protein muteins

17. 5,395,760, Mar. 7, 1995, DNA encoding tumor necrosis factor-.alpha. and -.beta. receptors; Craig A. Smith, et al., 435/240.1; 424/85.1; 435/69.4, 172.3; 530/351, 388.23; 536/23.51 [IMAGE AVAILABLE]

US PAT NO: 5,395,760 [IMAGE AVAILABLE] L2: 17 of 49
TITLE: DNA encoding tumor necrosis factor-.alpha. and -.beta. receptors

18. 5,391,725, Feb. 21, 1995, Organ-specific plant promoter sequences; Gloria M. Coruzzi, et al., 536/24.1; 435/69.1, 172.3, 320.1; 800/205; 935/35, 36 [IMAGE AVAILABLE]

US PAT NO: 5,391,725 [IMAGE AVAILABLE] L2: 18 of 49
TITLE: Organ-specific plant promoter sequences

19. 5,380,831, Jan. 10, 1995, Synthetic insecticidal crystal protein gene; Michael J. Adang, et al., 536/23.71; 435/69.1, 172.3; 800/205 [IMAGE AVAILABLE]

US PAT NO: 5,380,831 [IMAGE AVAILABLE] L2: 19 of 49
TITLE: Synthetic insecticidal crystal protein gene

20. 5,376,567, Dec. 27, 1994, Expression of interferon genes in Chinese hamster ovary cells; Francis P. McCormick, et al., 435/320.1; 424/85.4; 435/69.51, 91.41, 240.1, 252.3; 536/23.52; 935/23, 56 [IMAGE AVAILABLE]

US PAT NO: 5,376,567 [IMAGE AVAILABLE] L2: 20 of 49
TITLE: Expression of interferon genes in Chinese hamster ovary cells

21. 5,362,865, Nov. 8, 1994, Enhanced expression in plants using non-translated leader sequences; Glenn D. Austin, 536/24.1; 435/172.3, 240.4; 536/24.5 [IMAGE AVAILABLE]

US PAT NO: 5,362,865 [IMAGE AVAILABLE] L2: 21 of 49
TITLE: Enhanced expression in plants using non-translated leader sequences

22. 5,354,557, Oct. 11, 1994, Osteogenic devices; Hermann Oppermann, et al., 424/423, 422, 424, 426 [IMAGE AVAILABLE]

US PAT NO: 5,354,557 [IMAGE AVAILABLE] L2: 22 of 49
TITLE: Osteogenic devices

23. 5,350,683, Sep. 27, 1994, DNA encoding type II interleukin-1 receptors; John E. Sims, et al., 435/69.1, 252.3, 320.1; 530/350; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,350,683 [IMAGE AVAILABLE] L2: 23 of 49
TITLE: DNA encoding type II interleukin-1 receptors

24. 5,344,923, Sep. 6, 1994, Nucleotide sequence encoding for bifunctional enzyme for proline production; Desh P. S. Verma, et al., 536/23.2; 435/172.3; 536/23.6 [IMAGE AVAILABLE]

US PAT NO: 5,344,923 [IMAGE AVAILABLE] L2: 24 of 49
TITLE: Nucleotide sequence encoding for bifunctional enzyme for proline production

25. 5,334,529, Aug. 2, 1994, Stably transformed coffee plant cells and

plantlets; Tommy L. Adams, et al., 435/240.4, 240.47, 240.49; 800/205; 935/67 [IMAGE AVAILABLE]

US PAT NO: 5,334,529 [IMAGE AVAILABLE] L2: 25 of 49
TITLE: Stably transformed coffee plant cells and plantlets

26. 5,324,638, Jun. 28, 1994, Brain transcription factor, nucleic acids encoding same and uses thereof; Wufan Tao, et al., 435/69.1; 530/350; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,324,638 [IMAGE AVAILABLE] L2: 26 of 49
TITLE: Brain transcription factor, nucleic acids encoding same and uses thereof

27. 5,304,730, Apr. 19, 1994, Virus resistant plants and method therefore; Edgar C. Lawson, et al., 800/205; 435/172.3; 536/23.6, 23.72; 800/DIG.42; 935/10, 35, 64, 67 [IMAGE AVAILABLE]

US PAT NO: 5,304,730 [IMAGE AVAILABLE] L2: 27 of 49
TITLE: Virus resistant plants and method therefore

28. 5,284,755, Feb. 8, 1994, DNA encoding leukemia inhibitory factor receptors; David P. Gearing, et al., 435/69.1, 69.7, 252.3, 320.1; 536/23.4, 23.5 [IMAGE AVAILABLE]

US PAT NO: 5,284,755 [IMAGE AVAILABLE] L2: 28 of 49
TITLE: DNA encoding leukemia inhibitory factor receptors

29. 5,276,268, Jan. 4, 1994, Phosphinothricin-resistance gene, and its use; Eckhard Strauch, et al., 800/205; 435/172.3, 240.4, 252.3; 536/23.7; 800/255, DIG.43; 935/67 [IMAGE AVAILABLE]

US PAT NO: 5,276,268 [IMAGE AVAILABLE] L2: 29 of 49
TITLE: Phosphinothricin-resistance gene, and its use

30. 5,273,894, Dec. 28, 1993, Phosphinothricin-resistance gene, and its use; Eckhard Strauch, et al., 435/129, 128, 172.3, 193, 240.4, 252.3; 536/23.2, 23.7 [IMAGE AVAILABLE]

US PAT NO: 5,273,894 [IMAGE AVAILABLE] L2: 30 of 49
TITLE: Phosphinothricin-resistance gene, and its use

31. 5,266,683, Nov. 30, 1993, Osteogenic proteins; Hermann Oppermann, et al., 530/326, 327, 328, 350, 395, 840 [IMAGE AVAILABLE]

US PAT NO: 5,266,683 [IMAGE AVAILABLE] L2: 31 of 49
TITLE: Osteogenic proteins

32. 5,256,558, Oct. 26, 1993, Gene encoding plant asparagine synthetase; Gloria M. Coruzzi, et al., 435/240.1, 172.3, 252.3, 252.33, 320.1; 536/23.2, 24.1 [IMAGE AVAILABLE]

US PAT NO: 5,256,558 [IMAGE AVAILABLE] L2: 32 of 49
TITLE: Gene encoding plant asparagine synthetase

33. 5,145,777, Sep. 8, 1992, Plant cells resistant to herbicidal **glutamine** **synthetase** inhibitors; Howard M. Goodman, et al., 435/172.3, 69.1, 240.4, 320.1; 504/206, 319, 320, 322; 536/23.2, 23.6; 800/200, 205, 255; 935/33, 35 [IMAGE AVAILABLE]

US PAT NO: 5,145,777 [IMAGE AVAILABLE] L2: 33 of 49
TITLE: Plant cells resistant to herbicidal **glutamine**
synthetase inhibitors

34. 5,137,816, Aug. 11, 1992, Rhizobial diagnostic probes and rhizobium trifolii nifH promoters; Barry G. Rolfe, et al., 435/172.3, 252.2, 252.3, 320.1, 878; 536/23.6, 23.71; 935/41, 72 [IMAGE AVAILABLE]

US PAT NO: 5,137,816 [IMAGE AVAILABLE] L2: 34 of 49
TITLE: Rhizobial diagnostic probes and rhizobium trifolii nifH
promoters

35. 5,122,464, Jun. 16, 1992, Method for dominant selection in eucaryotic cells; Richard H. Wilson, et al., 435/172.3, 320.1 [IMAGE AVAILABLE]

US PAT NO: 5,122,464 [IMAGE AVAILABLE] L2: 35 of 49
TITLE: Method for dominant selection in eucaryotic cells

36. 5,098,838, Mar. 24, 1992, Expression of wild type and mutant **glutamine** **synthetase** in foreign hosts; Howard Goodman, et al., 435/183, 252.3, 252.33, 320.1; 536/23.2, 23.6; 935/10, 27, 29, 66, 67, 72, 73 [IMAGE AVAILABLE]

US PAT NO: 5,098,838 [IMAGE AVAILABLE] L2: 36 of 49
TITLE: Expression of wild type and mutant **glutamine**
synthetase in foreign hosts

37. 5,098,703, Mar. 24, 1992, Interferon-alpha 76; Michael A. Innis, 424/85.7; 435/69.51, 811; 530/351; 536/23.52 [IMAGE AVAILABLE]

US PAT NO: 5,098,703 [IMAGE AVAILABLE] L2: 37 of 49
TITLE: Interferon-alpha 76

38. 5,077,399, Dec. 31, 1991, Phosphinothricin-resistance gene; Dieter Brauer, et al., 536/23.7; 435/252.1, 320.1, 829 [IMAGE AVAILABLE]

US PAT NO: 5,077,399 [IMAGE AVAILABLE] L2: 38 of 49
TITLE: Phosphinothricin-resistance gene

39. 5,043,270, Aug. 27, 1991, Intronic overexpression **vectors**; John M. Abrams, et al., 435/69.1, 172.3, 240.1, 320.1; 536/23.2, 23.5; 935/34, 61, 66, 70, 71, 79, 84 [IMAGE AVAILABLE]

US PAT NO: 5,043,270 [IMAGE AVAILABLE] L2: 39 of 49
TITLE: Intronic overexpression **vectors**

40. 5,008,194, Apr. 16, 1991, nifH promoters of Bradyrhizobium; Barry G. Rolfe, et al., 435/172.3, 252.2, 252.3, 320.1; 536/23.6, 24.1; 935/6, 35, 41 [IMAGE AVAILABLE]

US PAT NO: 5,008,194 [IMAGE AVAILABLE] L2: 40 of 49
TITLE: nifH promoters of Bradyrhizobium

41. 5,001,061, Mar. 19, 1991, nifD promoter of Bradyrhizobium; Barry G. Rolfe, et al., 435/172.3, 252.2, 252.3, 320.1; 536/23.1, 23.6, 24.2; 935/6, 35, 41 [IMAGE AVAILABLE]

US PAT NO: 5,001,061 [IMAGE AVAILABLE] L2: 41 of 49
TITLE: nifD promoter of Bradyrhizobium

42. 4,975,374, Dec. 4, 1990, Expression of wild type and mutant **glutamine** **synthetase** in foreign hosts; Howard Goodman, et al., 435/172.3, 183, 252.3, 252.33; 536/23.2, 23.6; 935/14, 29, 30, 73 [IMAGE AVAILABLE]

US PAT NO: 4,975,374 [IMAGE AVAILABLE] L2: 42 of 49
TITLE: Expression of wild type and mutant **glutamine**
synthetase in foreign hosts

43. 4,975,276, Dec. 4, 1990, Interferon-alpha 54; Michael A. Innis, 424/85.7, 85.4; 435/69.51, 811; 530/351 [IMAGE AVAILABLE]

US PAT NO: 4,975,276 [IMAGE AVAILABLE] L2: 43 of 49
TITLE: Interferon-alpha 54

44. 4,973,479, Nov. 27, 1990, Interferon-.alpha.61; Michael A. Innis, 424/85.7, 85.4; 435/69.51, 811; 530/351 [IMAGE AVAILABLE]

US PAT NO: 4,973,479 [IMAGE AVAILABLE] L2: 44 of 49

TITLE: Interferon-.alpha.61

45. 4,966,843, Oct. 30, 1990, Expression of interferon genes in Chinese hamster ovary cells; Francis P. McCormick, et al., 435/69.51, 70.1, 70.3, 70.5, 172.1, 172.3, 240.2, 320.1, 811; 536/23.5, 23.52, 24.1; 935/11, 34, 70 [IMAGE AVAILABLE]

US PAT NO: 4,966,843 [IMAGE AVAILABLE] L2: 45 of 49
TITLE: Expression of interferon genes in Chinese hamster ovary cells

46. 4,956,288, Sep. 11, 1990, Method for producing cells containing stably integrated foreign DNA at a high copy number, the cells produced by this method, and the use of these cells to produce the polypeptides coded for by the foreign DNA; James G. Barsoum, 435/172.3, 69.1, 70.1, 71.1, 172.1, 252.3; 935/16, 33, 52 [IMAGE AVAILABLE]

US PAT NO: 4,956,288 [IMAGE AVAILABLE] L2: 46 of 49
TITLE: Method for producing cells containing stably integrated foreign DNA at a high copy number, the cells produced by this method, and the use of these cells to produce the polypeptides coded for by the foreign DNA

47. 4,803,165, Feb. 7, 1989, Nif promoter of fast-growing rhizobium japonicum; Edward R. Appelbaum, 435/172.3, 69.1, 252.2, 252.33, 320.1; 536/23.6, 23.7, 23.71, 24.1; 935/29, 30, 41, 56, 64, 67, 72 [IMAGE AVAILABLE]

US PAT NO: 4,803,165 [IMAGE AVAILABLE] L2: 47 of 49
TITLE: Nif promoter of fast-growing rhizobium japonicum

48. 4,782,022, Nov. 1, 1988, Nitrogen fixation regulator genes; Alfred Puhler, et al., 435/172.3, 252.2, 252.33, 320.1; 536/23.2, 23.6, 23.71, 24.1; 930/200; 935/29, 56, 72 [IMAGE AVAILABLE]

US PAT NO: 4,782,022 [IMAGE AVAILABLE] L2: 48 of 49
TITLE: Nitrogen fixation regulator genes

49. 4,594,323, Jun. 10, 1986, Hybrid DNA conferring osmotic tolerance; Laszlo N. Csonka, et al., 435/172.3, 107, 252.3, 320.1; 536/23.2; 935/14, 29, 60 [IMAGE AVAILABLE]

US PAT NO: 4,594,323 [IMAGE AVAILABLE] L2: 49 of 49
TITLE: Hybrid DNA conferring osmotic tolerance
=> d fro,39,42

US PAT NO: 5,043,270 [IMAGE AVAILABLE] L2: 39 of 49
DATE ISSUED: Aug. 27, 1991
TITLE: Intronic overexpression **vectors**
INVENTOR: John M. Abrams, New York, NY
Robert T. Schimke, Palo Alto, CA
Susan M. Thorpe, Copenhagen, Denmark
ASSIGNEE: The Board of Trustees of the Leland Stanford Junior
University, Stanford, CA (U.S. corp.)
APPL-NO: 07/331,434
DATE FILED: Mar. 31, 1989
INT-CL: [5] C12N 1/00; C12N 15/12; C12N 15/11; C12N 5/00
US-CL-ISSUED: 435/69.1, 172.3, 240.1, 320.1; 536/27; 935/34, 61, 66, 70,
71, 79, 84
US-CL-CURRENT: 435/69.1, 172.3, 240.1, 320.1; 536/23.2, 23.5; 935/34, 61,
66, 70, 71, 79, 84
SEARCH-FLD: 435/69.1, 70.1, 70.3, 172.1, 172.3, 240.1, 240.2, 320,
320.1; 536/27; 935/22, 29, 34, 42, 61, 66, 70, 71, 79,
84
REF-CITED:

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Alteration in Oncogenic Alleles" Hung et al., (1986) Proc. Natl. Acad.
Sci. USA, 83: 261-264.
"Gene Within a Gene: Nested Drosophila Genes Encode Unrelated Proteins on
Opposite DNA Strands" Henikoff et al., (1986) Cell, 44: 33-42.
"Methotrexate-Induced Amplification of the Bovine Lutropin Genes in
Chinese Hamster Ovary Cells" Kaetzel et al., (1988) Journal of
Biological Chemistry, 263: 6344-6351.
"Coamplification and Coexpression of Human Tissue-Type Plasminogen
Activator and Murine Dihydrofolate Reductase Sequences in Chinese
Hamster Ovary Cells" Kaufman et al. (1985) Molecular and Cellular
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"Competitive Inhibition of hsp70 Gene Expression Causes
Thermosensitivity" Johnston et al., (1988) Science, 242: 1551-1554.
"Amplification and Expression of Sequences Cotransfected with a Modular
Dihydrofolate Reductase Complementary DNA Gene" Kaufman et al., (1982)
Journal of Molecular Biology, 159: 601-621.
ART-UNIT: 185
PRIM-EXMR: James Martinell
LEGAL-REP: Bertram I. Rowland

ABSTRACT:

DNA constructs are provided employing intronically positioned expression,

systems, where one of the genes is a dominant gene, usually amplifiable, and the other gene encodes a sequence of interest. Higher levels of co-expression are achieved than when the genes are ligated in tandem. Specifically, the gene of interest is inserted into the intron of a DHFR minigene, the construct transformed into a mammalian cell and the resulting transformants stressed with progressively increasing levels of methotrexate. Substantially increasing levels of co-expression are achieved with increasing levels of methotrexate.

26 Claims, No Drawings

US PAT NO: 4,975,374 [IMAGE AVAILABLE] L2: 42 of 49
DATE ISSUED: Dec. 4, 1990
TITLE: Expression of wild type and mutant **glutamine**
 synthetase in foreign hosts
INVENTOR: Howard Goodman, Newton, MA
 Shiladitya DasSarma, Amherst, MA
 Edmund Tischer, Palo Alto, CA
 Theresa K. Peterman, Cambridge, MA
ASSIGNEE: The General Hospital Corporation, Boston, MA (U.S. corp.)
APPL-NO: 07/010,612
DATE FILED: Feb. 4, 1987
INT-CL: [5] C12N 15/00; C12N 9/00; C12N 1/20; C07H 15/12
US-CL-ISSUED: 435/172.3, 183, 252.3, 252.33, 320; 536/27; 935/14, 29,
 30, 73
US-CL-CURRENT: 435/172.3, 183, 252.3, 252.33; 536/23.2, 23.6; 935/14, 29,
 30, 73
SEARCH-FLD: 435/183, 240.46, 252.33, 320; 536/27; 935/14
REF-CITED:

U.S. PATENT DOCUMENTS

4,594,323 6/1986 Csonka et al. 435/107

FOREIGN PATENT DOCUMENTS

86/02097 4/1986 World Intellectual Property Organization 19/34

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Botstein et al., Science 229:1193-1201 (1985).
Coulondre et al., J. Mol. Biol. 117:525-575 (1977).
European Search Report for Corresponding Application EPO 87103936.
ART-UNIT: 185
PRIM-EXMR: Thomas D. Mays
LEGAL-REP: Saidman, Sterne, Kessler & Goldstein

ABSTRACT:

The invention relates to a mutant **glutamine** **synthetase** (GS) enzyme which is resistant to inhibition by herbicidal GS inhibitors, such as phosphinothricin (PPT), genetic sequences coding therefor, plants cells and prokaryotes transformed with the genetic sequences, and herbicidal GS inhibitor-resistant plant cells and plants.

30 Claims, 16 Drawing Figures

=> d 42,clms

US PAT NO: 4,975,374 [IMAGE AVAILABLE] L2: 42 of 49

CLAIMS:

CLMS(1)

We claim:

1. A mutant alfalfa **glutamine** **synthetase** enzyme which is resistant to inhibition by a herbicidal **glutamine** **synthetase** inhibitor.

CLMS(2)

2. A mutant alfalfa **glutamine** **synthetase** enzyme which is resistant to inhibition by a herbicidal **glutamine** **synthetase** inhibitor wherein said **glutamine** **synthetase** enzyme has the following amino acid sequence:

1 M S L L S D L I N L D L S E T T E K I I
21
A E Y I W I G G S G L D L R S K A R T
L
41
P G P V T D P S Q L P K W N Y D G S S
T

61
 G Q A P G E D S E V I I Y P Q A I F K
 D

81
 P F R R G N N I L V M C D A Y T P A G
 E

101
 P I P T N K R H A A A K I F S H P D V
 V

121
 A E V P W Y G I E Q E Y T L L Q K D I
 N

141
 W P L G W P V G G F P G P Q G P Y Y C
 G

161
 A G A D K A F G R D I V D S H Y K A C
 L

181
 Y A G I N I S G I N G E V M P G Q W E
 F

201
 Q V G P S V X.^{sup.1}
 I S A G D E I W V A R Y
 I

221
 L E R I T E V A G V V L S F D P K P I
 K

241
 G D W N X.^{sup.2}
 A G A H T N Y S T K S M R E
 D

261
 G G Y E V I L K A I E K L G K K H K E
 H

281
 I A A Y G E G N E R R L T G R H E T A
 D

301
 I N T F L W G V A N R G A S I R V G R
 D

321
 T E K A G K G Y F E D X.^{sup.3}
 R P S S N M D
 P

341
 Y V V T S M I A D T T I L W K P

where x.sup.1 at 207 is G;

X.sup.2 at 245 represents an amino acid other than glycine; and

X.sup.3 at 332 is arginine or lysine.

CLMS(3)

3. The mutant alfalfa **glutamine** **synthetase** of claim 2 wherein said X.sup.2 is neutral or basic.

CLMS(4)

4. The mutant alfalfa **glutamine** **synthetase** of claim 2 wherein said X.sub.2 is selected from the group consisting of serine, arginine, and cysteine.

CLMS(5)

5. The mutant alfalfa **glutamine** **synthetase** of claim 2, wherein said X.sup.3 is lysine.

CLMS(6)

6. A mutant alfalfa **glutamine** **synthetase** enzyme which is resistant to inhibition by a herbicidal **glutamine** **synthetase** inhibitor, wherein said enzyme lacks the four native N-terminal amino acid residues 2 to 5, inclusive.

CLMS(7)

7. A mutant alfalfa **glutamine** **synthetase** enzyme which is resistant to inhibition by a herbicidal **glutamine** **synthetase** inhibitor, wherein said enzyme has the formula:

1 M S L L S D L I N L D L S E T T E K I I
21
A E Y I W I G G S G L D L R S K A R T
L
41
P G P V T D P S Q L P K W N Y D G S S
T
61
G Q A P G E D S E V I I Y P Q A I F K
D

81 P F R R G N N I L V M C D A Y T P A G
 E
 101 P I P T N K R H A A A K I F S H P D V
 V
 121 A E V P W Y G I E Q E Y T L L Q K D I
 N
 141 W P L G W P V G G F P G P Q G P Y Y C
 G
 161 A G A D K A F G R D I V D S H Y K A C
 L
 181 Y A G I N I S G I N G E V M P G Q W E
 F
 201 Q V G P S V X.^{sup.1}
 I S A G D E I W V A R Y
 I
 221 L E R I T E V A G V V L S F D P K P I
 K
 241 G D W N X.^{sup.2}
 A G A H T N Y S T K S M R E
 D
 261 G G Y E V I L K A I E K L G K K H K E
 H
 281 I A A Y G E G N E R R L T G R H E T A
 D
 301 I N T F L W G V A N R G A S I R V G R
 D
 321 T E K A G K G Y F E D X.^{sup.3}
 R P S S N M D
 P
 341 Y V V T S M I A D T T I L W K P

where X.^{sup.1} at 207 is G;

X.sup.2 at 245 represents an amino acid other than glycine; and
X.sup.3 at 332 is lysine; and wherein said enzyme lacks the four native
N-terminal amino acid residues 2 to 5, inclusive.

CLMS(8)

8. A mutant alfalfa ****glutamine**** ****synthetase**** enzyme having the
following amino acid sequence:

```
1 M S L L S D L I N L D L S E T T E K I I
21  A E Y I W I G G S G L D L R S K A R      T
    L
41  P G P V T D P S Q L P K W N Y D G S      S
    T
61  G Q A P G E D S E V I I Y P Q A I F      K
    D
81  P F R R G N N I L V M C D A Y T P A      G
    E
101 P I P T N K R H A A A K I F S H P D      V
    V
121 A E V P W Y G I E Q E Y T L L Q K D      I
    N
141 W P L G W P V G G F P G P Q G P Y Y      C
    G
161 A G A D K A F G R D I V D S H Y K A      C
    L
181 Y A G I N I S G I N G E V M P G Q W      E
    F
201 Q V G P S V X.sup.1
    I S A G D E I W V A R      Y
    I
221 L E R I T E V A G V V L S F D P K P      I
    K
241
```

G D W N X.²
 A G A H T N Y S T K S M R E
 D
 261
 G G Y E V I L K A I E K L G K K H K E
 H
 281
 I A A Y G E G N E R R L T G R H E T A
 D
 301
 I N T F L W G V A N R G A S I R V G R
 D
 321
 T E K A G K G Y F E D X.³
 R P S S N M D
 P
 341
 Y V V T S M I A D T T I L W K P

— where X.¹ at 207 is G;
 X.² at 245 represents an amino acid other than glycine;
 X.³ at 332 is arginine or lysine; and
 wherein said amino acid sequence lacks the methionine residue at
 position 1.

CLMS(9)

9. The ****glutamine** synthetase**** of claim 1, wherein said inhibitor is phosphinothricin.

CLMS(10)

10. A nucleic acid molecule coding for a mutant alfalfa ****glutamine** synthetase**** enzyme which is resistant to inhibition by a herbicidal ****glutamine** synthetase**** inhibitor.

CLMS(11)

11. The nucleic acid molecule of claim 10, which is the following:
 ##STR1## wherein X.⁴ is a triplet which codes for gly; X.⁵ is a
 triplet which codes for an amino acid other than glycine; and
 X.⁶ is a triplet which codes for arginine or lysine.

CLMS(12)

12. The nucleic acid molecule of claim 11, wherein said amino acid

encoded by X.sup.5 is neutral or basic.

CLMS(13)

13. The nucleic acid molecule of claim 11, wherein said amino acid encoded by X.sup.5 is selected from the group consisting of serine, arginine, or cysteine.

CLMS(14)

14. The nucleic acid molecule of claim 11, wherein said X.sup.6 is a triplet which codes for lysine.

CLMS(15)

15. A nucleic acid molecule coding for a mutant alfalfa **glutamine** **synthetase** enzyme which is resistant to inhibition by a herbicidal **glutamine** **synthetase** inhibitor, wherein said nucleic acid sequence further comprises an ATG codon prior to the codon for the first N-terminal amino acid residue.

CLMS(16)

16. The nucleic acid molecule of claim 10, wherein said inhibitor is phosphinothricin.

CLMS(17)

17. A recombinant DNA molecule comprising a nucleotide sequence coding for a mutant alfalfa **glutamine** **synthetase** enzyme which is resistant to inhibition by a herbicidal **glutamine** **synthetase** inhibitor.

CLMS(18)

18. The recombinant DNA molecule of claim 17, which is a plasmid.

CLMS(19)

19. The recombinant DNA molecule of claim 18, wherein said nucleotide sequence is in operable linkage and expressible by a prokaryotic promoter, and further comprising a prokaryotic origin of replication, wherein when a prokaryote is transformed with said plasmid, said plasmid replicates.

CLMS(20)

20. The plasmid of claim 19, which is the Ti plasmid of *Agrobacterium tumefaciens*.

CLMS (21)

21. The recombinant DNA molecule of claim 19, wherein said nucleotide sequence is in further operable linkage with and expressible by a transcription promoter for the expression of said ****glutamine**** ****synthetase**** sequence in a plant cell.

CLMS (22)

22. A host cell transformed by the recombinant DNA molecule of claim 17.

CLMS (23)

23. The host cell of claim 22 which is a prokaryotic microorganism.

CLMS (24)

24. The host cell of claim 22, which is a plant cell.

CLMS (25)

25. A plasmid comprising a prokaryotic origin of replication, a prokaryotic promoter, and a nucleotide sequence coding for a mutant alfalfa ****glutamine**** ****synthetase**** enzyme which is resistant to inhibition by a herbicidal ****glutamine**** ****synthetase**** inhibitor, wherein when a prokaryotic host is transformed with said plasmid, said plasmid replicates and said enzyme is expressible.

CLMS (26)

26. A prokaryotic transformed with a recombinant DNA molecule comprising a nucleotide sequence coding for a mutant alfalfa ****glutamine**** ****synthetase**** enzyme which is resistant to inhibition by a herbicidal ****glutamine**** ****synthetase**** inhibitor.

CLMS (27)

27. The prokaryotic of claim 26, wherein said recombinant DNA molecule is a plasmid.

CLMS (28)

28. The prokaryotic of claim 27, which is a bacterium which, in its untransformed state, is incapable of producing the functional wildtype

bacterial **glutamine** **synthetase**.

CLMS(29)

29. The prokaryotic of claim 28, which is a mutant bacterium which, in its untransformed state, exhibits diminished **glutamine** **synthetase** activity in comparison to the wild type bacterium.

CLMS(30)

30. The prokaryotic as in any of claims 26, 28 or 29, which is E. coli.
=

?begin 5,6,55,154,155,156,312,399,biotech,biosci

?s glutamine synthetase

S1 3971 GLUTAMINE SYNTHETASE

?s s1 and amplif?

3971 S1

405653 AMPLIF?

S2 32 S1 AND AMPLIF?

?rd s2

>>>Duplicate detection is not supported for File 42.
>>>Duplicate detection is not supported for File 43.
>>>Duplicate detection is not supported for File 94.
>>>Duplicate detection is not supported for File 129.
>>>Duplicate detection is not supported for File 130.
>>>Duplicate detection is not supported for File 140.
>>>Duplicate detection is not supported for File 158.
>>>Duplicate detection is not supported for File 187.
>>>Duplicate detection is not supported for File 286.
>>>Duplicate detection is not supported for File 446.
>>>Duplicate detection is not supported for File 449.
>>>Duplicate detection is not supported for File 452.
>>>Duplicate detection is not supported for File 455.
>>>Duplicate detection is not supported for File 456.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records

S3 28 RD S2 (unique items)

?d s3/3/1-28

Display 3/3/1 (Item 1 from file: 73)

DIALOG(R)File 73:EMBASE

(c) 1996 Elsevier Science B.V. All rts. reserv.

5500453 EMBASE No: 83252276

Mouse 3T6 cells that overproduce glutamine synthetase

Young A.P.; Ringold G.M.

Dep. Pharmacol., Stanford Univ. Sch. Med., Stanford, CA 94305 USA

J. BIOL. CHEM. (USA) , 1983, 258/18 (11260-11266) CODEN: JBCHA

LANGUAGES: ENGLISH

- end of record -

?

Display 3/3/2 (Item 2 from file: 73)

DIALOG(R)File 73:EMBASE

(c) 1996 Elsevier Science B.V. All rts. reserv.

1176031 EMBASE No: 78354402

The location of glutamine synthetase within the rat and rabbit nephron

Burch H.B.; Choi S.; McCarthy W.Z.; et al.

Dept. Pharmacol., Washington Univ. Sch. Med., St Louis, Mo. 63110 USA

BIOCHEM. BIOPHYS. RES. COMMUN. (USA) , 1978, 82/2 (498-505) CODEN: BBRCA

LANGUAGES: ENGLISH

- end of record -

?

Display 3/3/3 (Item 1 from file: 76)

DIALOG(R)File 76:Life Sciences Collection

(c) 1996 Cambridge Sci Abs. All rts. reserv.

01782836 3551832

Genetic and biochemical characterization of the two glutamine synthetases

GSI and GSII of the phosphinothricyl-alanyl-alanine producer,

Streptomyces viridochromogenes Tue494

Hillemann, D.; Dammann, T.; Hillemann, A.; Wohlleben, W.

Univ. Saarlandes, Abt. Angew. Molekularbiol., D-66041 Saarbruecken, FRG

J. GEN. MICROBIOL. vol. 139, no. 8, pp. 1773-1783 (1993)

ISSN: 0001-8277

DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH

SUBFILE: Microbiology Abstracts B: Bacteriology; Genetics Abstracts

- end of record -

?

Display 3/3/4 (Item 2 from file: 76)

DIALOG(R)File 76:Life Sciences Collection

(c) 1996 Cambridge Sci Abs. All rts. reserv.

01719118 3005876

Process development for the production of recombinant antibodies using the
glutamine synthetase (GS) system.

Brown, M.E.; Renner, G.; Field, R.P.; Hassell, T.

Celltech Ltd., 216 Bath Rd., Slough, Berks. SL1 4EN, UK

CYTOTECHNOLOGY. vol. 9, no. 1-3, pp. 231-236 (1992.)

ISSN: 0920-9069

DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH

NOTES: Cell Culture Engineering III.

SUBFILE: Medical & Pharmaceutical Biotechnology Abstracts

- end of record -

?

Display 3/3/5 (Item 3 from file: 76)
DIALOG(R)File 76:Life Sciences Collection
(c) 1996 Cambridge Sci Abs. All rts. reserv.

01047101 1548124

Gene amplification: The Chinese hamster glutamine synthetase gene.
Sanders, P.G.; Hussein, A.; Coggins, L.; Wilson, R.

Dep. Genet., Univ. Glasgow, Glasgow G11 5JS, UK

ADVANCES IN ANIMAL CELL TECHNOLOGY: CELL ENGINEERING, EVALUATION AND
EXPLOITATION.

Spier, R.; Hennesen, W. (eds.)

ISBN: 3-8055-4556-8

DEV. BIOL. STAND. vol. 66 pp. 55-63 (1987.)

CONFERENCE: 7. General Meeting of ESACT on Animal Cell Technology: Cell
Engineering, Evaluation and Exploitation, Baden (Austria), 1985 Sep
30-Oct 4

DOCUMENT TYPE: Book; Conference paper; Journal LANGUAGE: ENGLISH

SUBFILE: Biotechnology Abstracts; Biochemistry Abstracts Part 2: Nucleic
Acids; Genetics Abstracts

- end of record -

?

Display 3/3/6 (Item 4 from file: 76)
DIALOG(R)File 76:Life Sciences Collection
(c) 1996 Cambridge Sci Abs. All rts. reserv.

00877896 1046233

Herbicide-resistant alfalfa cells: An example of gene amplification in
plants.

Donn, G.; Tischer, E.; Smith, J.A.; Goodman, H.M.

Dep. Mol. Biol., Massachusetts Gen. Hosp., Boston, MA 02114, USA

J. MOL. APPL. GENET. vol. 2, no. 6, pp. 621-635 (1984.)

DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH

SUBFILE: Genetics Abstracts; Biochemistry Abstracts Part 2: Nucleic Acids;
Biotechnology Abstracts; Biochemistry Abstracts Part 3: Amino Acids,
Peptides and Proteins

- end of record -

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Display 3/3/7 (Item 5 from file: 76)
DIALOG(R)File 76:Life Sciences Collection
(c) 1996 Cambridge Sci Abs. All rts. reserv.

00722221 0646394

Amplification and cloning of the Chinese hamster glutamine synthetase gene.

Sanders, P.G.; Wilson, R.H.

Inst. Genet., Univ. Glasgow, Glasgow G11 5JS, UK

EMBO J. vol. 3, no. 1, pp. 65-71 (1984.)

DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH

SUBFILE: Genetics Abstracts; Biochemistry Abstracts Part 2: Nucleic Acids

- end of record -

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Display 3/3/8 (Item 1 from file: 94)

DIALOG(R)File 94:JICST-EPlus

(c) 1996 Japan Info Center of Sci & Tech. All rts. reserv.

02625246 JICST ACCESSION NUMBER: 95A0153214 FILE SEGMENT: JICST-E

Central mechanism of a novel neurotoxin, paraquat, and its relationship to increased amounts of excitatory amino acids.

KISO K (1); WATANABE Y (1); SHIBUYA T (1)

(1) Tokyo Medical Coll., Tokyo, JPN

Neurosciences, 1994, VOL.20,NO.4, PAGE.169-179, FIG.4, REF.34

JOURNAL NUMBER: Z0398BAE ISSN NO: 0388-7448

UNIVERSAL DECIMAL CLASSIFICATION: 632.951 591.18.05+591.481

LANGUAGE: English COUNTRY OF PUBLICATION: Japan

DOCUMENT TYPE: Journal

ARTICLE TYPE: Original paper

MEDIA TYPE: Printed Publication

- end of record -

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Display 3/3/9 (Item 2 from file: 94)

DIALOG(R)File 94:JICST-EPlus

(c) 1996 Japan Info Center of Sci & Tech. All rts. reserv.

00828995 JICST ACCESSION NUMBER: 89A0223103 FILE SEGMENT: JICST-E

Thermophilic enzymes from thermophiles and their utilization to biosensing.

IIDA TAKEAKI (1)

(1) Saitama Univ., Faculty of Engineering

Bio Ind, 1989, VOL.6,NO.1, PAGE.53-61, FIG.7, TBL.2, REF.15

JOURNAL NUMBER: Y0746AAL ISSN NO: 0910-6545

UNIVERSAL DECIMAL CLASSIFICATION: 577.15:574.6 576.8.095:577.151

LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan

DOCUMENT TYPE: Journal

ARTICLE TYPE: Commentary

- end of record -

?

Display 3/3/10 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

10714100 PASCAL No.: 93-0223414
Characterization of the glutamine synthetase amplifiable eukaryotic
expression system applied to an integral membrane protein : the human
thyrotropin receptor
HARFST E; JOHNSTONE A P
Saint George's hosp. medical school, dep. cellular molecular sci., London
SW17 0RE, United Kingdom
Journal: Analytical biochemistry, 1992, 207 (1) 80-84
Language: English

- end of record -

?

Display 3/3/11 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

10107619 PASCAL No.: 92-0313238
High-level expression of a recombinant antibody from myeloma cells using
a glutamine synthetase gene as an amplifiable selectable marker
BEBBINGTON C R; RENNER G; THOMSON S; KING D; ABRAMS D; YARRANTON G T
Celltech Ltd, Slough SL1 4EN, United Kingdom
Journal: Bio/technology - Nature Publishing Company, 1992, 10 (2)
169-175
Language: English

- end of record -

?

Display 3/3/12 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

09305802 PASCAL No.: 91-0096176
High level expression of tissue inhibitor of metalloproteinases in
chinese hamster ovary cells using glutamine synthetase gene amplification
COCKETT M I; BEBBINGTON C R; YARRANTON G T
Celltech Ltd, Slough Berks. SL1 4EN, United Kingdom
Journal: Bio/technology Nature Publishing Company, 1990, 8 (7) 662-667
Language: English

- end of record -

?

Display 3/3/13 (Item 4 from file: 144)
DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

08542020 PASCAL No.: 89-0090966

Dominant expression of a gene amplification-related herbicide resistance
in medicago cell hybrids

DEAK M; DONN G; FEHER A; DUDITS D

Hungarian acad. sci., inst. genetics, Szeged, Hungary

Journal: Plant cell reports, 1988, 7 (3) 158-161

Language: English

- end of record -

?